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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| LIETO, LOUIS D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/381,344 | SEEMANN ET AL. | |
| | Examiner | Art Unit | |
| | Louis D. Lieto | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5-32* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-18, 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 5/10/2004 is acknowledged. Claims 5-32 are pending. Claims 1 and 4 have been cancelled, claims 5,9,11,12 and 16 have been amended, and new claims 23-32 have been added. Claims 19-22 remain withdrawn from consideration. Please note that the examiner of record has changed to Dr. Louis Lieto of ART Unit 1632. Claims 5-18 and 23-32 are under consideration. The sections of 35 U.S.C. not included in this office action can be found in a previous office action. An action on the merits follows.

### *Claim Rejections - 35 USC § 112*

Claims 5-18 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the previous office action of 5/10/2004. Claims 1 and 4 have been canceled. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided.

New claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the tolerance of a mammal to transgenic cells, wherein the transgenic cells are produced in vivo after the administration of a vector carrying a transgene, by administering p15-deoxyspergualin to the mammal intravenously or intraperitoneally, before, during or after the administration of the vector, wherein said

transgene encodes a protein, wherein a concomitant immunosuppressant therapy is discontinued, does not reasonably provide enablement for increasing tolerance in a mammal to transgenic cells produced in vitro or wherein the transgene of the transgenic cells produces a therapeutic protein that effects a treatment of a disease or wherein the transgenic cell produced in vivo after administration of a vector in vivo produce treatment of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. New claims 23-32 are rejected for the reasons of record stated in the prior office action and as discussed below. The rejection of new claims 23-32 is necessitated by their addition.

Applicant's arguments filed 5/10/2004 have been fully considered but they are not persuasive. The previous office action identified the following issues of record: **1)** lack of enablement for administration of, or increasing the tolerance of, transgenic cells in any mammal including a man wherein the transgenic cells were from the same or different species expressed any gene or where the method was for treating any disease by gene therapy or by ex vivo cell therapy; **2)** lack of enabling disclosure for how a transgenic cells would be prepared in vitro or how a transgenic cell would be administered to a mammal or what doses of the cell would be used; **3)** lack of enabling disclosure for increasing tolerance in a mammal to transgenic cells because of incongruities in examples 1 and 2 of the specification indicating that the protection produced is all because of the protein product antigenicity or because of the adenoviral antigenicity; **4)** lack of enabling disclosure as to how the methods of treatment of diabetes or AIDS, or DNA vaccination would be carried out, or what doses of the DSG would be used or what routes of administration would be used or which transgene would be used such that the

effect of the transgene induced immune response is decreased by DSG treatment; **5)** lack of enablement for the claimed method when transgenic cells are transplanted in a mammal or in a man, except for autologous cell transplantation which would produce minimal immune response; and **6)** lack of enablement for a method of gene therapy.

**1 &5)** The rejections of record based on issues **1** and **5** are so closely related they will be treated together. Applicant has amended claim 16 to read only on transgenic cells derived from the same mammal in which they are transplanted. However, new claims 23-27 and 29-32 encompass transgenic cells from the same or different species. For the reasons of record stated in the previous action the rejection over issues **1** and **5** are maintained.

**2)** Applicant has not provided any arguments traversing the issue of lack of enabling disclosure for how a transgenic cells would be prepared in vitro or how a transgenic cell would be administered to a mammal or what doses of the cell would be used. While the applicant has amended claim 16 to read only on the administration of autologous cells, new claims 23-27 and 29-32 encompass transgenic cells from the same or different species. Further, the claims continue to encompass any method of preparing transgenic cells *in vitro* or any method of administering transgenic cells at any dosage. For these reasons of record and those stated in the previous action the rejection over issue **2** is maintained.

**3)** Applicant's arguments were found to be persuasive in overcoming the grounds of rejection based in issue **3**. Therefore the rejection based on issue **3** is withdrawn.

**4)** Applicant argues that the specification describes two methods of administering DSG in examples 1 and 2 and therefore satisfies the enablement requirement for any route of administration of DSG. The claim encompass any route of administration of DSG in any amount

over any time frame in conjunction, or before or after any transgene is administered in any amount, over any time frame to treat any disease. It is noted that the applicant has not provided any specific arguments rebutting the lack of enabling disclosure as to how the methods of treatment of diabetes or AIDS, or DNA vaccination would be carried out in regard to what routes of administration would be used or which transgene would be used such that the effect of the transgene induced immune response is decreased by DSG treatment. These issues are closely related to the problems related to a method of gene therapy, which is addressed below in issue **6**. Further, examples 1 and 2 do not provide any guidance on the treatment of any disease in regards to the time frame of DSG administration, the amounts of DSG to be administered and whether the timing or dosage of DSG must be varied to account for differences in the transgene to administered, the vector comprising the transgene, the gene therapy target or the route of transgene administration. None of these questions can be predictably addressed based on the working examples disclosed in the specification and the lack of specific guidance in the specification. For these reasons of record and those stated in the previous action the rejection over issue **4** is maintained.

**6)** Applicant argues that the examiners rejection of the claims directed to gene therapy treatments and treatments of diseases using gene therapy are without basis. Applicant further argues that gene therapy protocols are widely available. Finally, Applicant argues that a gene therapy treatment does not require a patient to be cured, and that even a low expression of a therapeutically useful gene may be of significant benefit to a patient. Applicant then cites Example 2, wherein AAT was shown to be expressed at increased and sustained levels after treatment with DSG. There are several problems with this argument. First, applicant's claims

read on the administration of any transgene as part of a method of gene therapy and their working examples are limited to the expression of β-Galactosidase and AAT in mice. For the reasons stated in the prior office action and reiterated below showing that these two genes can be expressed in mice does not enable a method of gene therapy for any transgene in any mammal for treating a disease. Second, the specification does not provide any evidence that the expression of a transgene, such as AAT, can be used to treat any disease in any mammal, even mice. The term treatment requires that their be some positive benefit to a mammal that is afflicted with a relevant disease. Neither the specification nor the applicant's arguments provide any evidence that expressing increased levels of AAT in a mouse provides a positive benefit to any mice afflicted with any disease. Third, methods of gene therapy remain unpredictable in the art. While many gene therapy protocols may be widely available there are substantial problems with reproducing results in different species using different vectors and/or transgenes and a method developed to treat on condition may not be applied to treat another disease.

***Rejections based the second paragraph of 35 U.S.C. 112***

The rejection of amended claim 16 under 35 U.S.C 112, second paragraph for being vague and indefinite is maintained in part. New claims 23-32 and amended claims 5-15, 17, 18 are also rejected over the same issues stated in the prior office action and as discussed below. The rejection of new claims 23-32 is necessitated by their addition, The rejection of amended claims 5-15, 17, 18 is necessitated by their amendment. Claims 1 and 4 have been canceled.

Applicant's arguments filed 5/10/2004 have been fully considered but they are not persuasive.

The rejection of claim 16 over being indefinite because it is unclear as to whether p15-deoxyspergualin is administered after discontinuing immunosuppressant therapy is withdrawn in view of applicant's amendment to claim 16.

The rejection of claim 16 over being vague and indefinite because it is unclear as to what is the invention claimed since the claim starts with "In a method..." and then recites the method is withdrawn in view of applicant's amendment to claim 16.

The rejection of claim 16 over being vague and indefinite because the term "the improvement" lacks antecedent basis is withdrawn in view of applicant's amendment to claim 16.

The rejection of claim 16 over being vague and indefinite is maintained because it recites the term "the improvement" without antecedent basis for the term, since no such term was recited before. Additionally, the rejection of claim 16 as being indefinite and unclear, is maintained because it is unclear as to how can an improvement can comprise administration of something. Further, the rejections are extended to claims 5-15, 17-18, which have been amended to depend on claim 16 and to new claims 23-25 and 28, which depend on claim 16.

Applicant argues that examples 1 and 2 provide various examples of when the immunosuppressant therapy is to be discontinued. However, since the claims encompass administering DSG with any transgenic cell from any species as a method of *ex vivo* therapy, as well as administering DSG with any transgene as a method of gene therapy it is not clear from the specification when the DSG is to be discontinued under either method. For these reasons of record and those stated in the previous action the rejection over this issue is maintained.

*Claim Rejections - 35 USC § 102*

The rejection of amended claims 1, 4, 9, 10, and 12 under 35 U.S.C 102 (a) is withdrawn. Applicant's amendments and arguments have been considered and have been found persuasive fully overcoming the grounds of rejection of claims 9, 10, and 12. Claims 1 and 4 have been cancelled.

New claims 26 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (Gene Therapy 3:496-502, 1996; abstract only).

Smith et al teach use of transient immunosuppression with DSG in mice injected intravenously with adenoviral vector carrying the beta-galactosidase gene. Smith et al administered DSG intravenously to the mice at time of the exposure of the adenovirus (see the abstract) first time and observed that administration of DSG permitted an effective second administration of a factor IX vector, without any immunosuppression afterwards.

Accordingly, the claimed invention is anticipated by Smith et al.

New claims 26 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Trapnell et al (WO 96/12406, 05-02-1996).

Trapnell et al teaches a method of administering a host concurrently with an adenoviral vector that expresses a therapeutic gene of interest and immunosuppressive agents, such as DSG (see the entire document). Example 3 discloses administration of DSG i.p. once daily beginning the day before administration and continuing for a total of eight days (see page 33, last paragraph). Figure 17 of Trapnell et al shows the human factor IX levels in mice that were administered adenoviral vector expressing factor IX alone or along with DSG or other

immunosuppressants. Page 42 (last paragraph) discloses that five weeks after vector administration, no detectable levels of neutralizing antibodies were observed. Trapnell et al also discloses that DSG immunosuppression also allows readministration of the adenoviral vector (see the last paragraph on page 44 continued on page 45). Claim 1 of Trapnell et al recites a method of gene therapy treatment by administering to a host an adenoviral vector including at least one DNA sequence encoding a therapeutic protein and an immunosuppressive agent and discontinuing administration of said adenoviral vector and said immunosuppressive agent. Claims 10-11, and 14 recite that the immunosuppressive agent is DSG. Claims 19-21 recite that the immunosuppressive agent is administered prior to, at the same time or after the administration of the adenoviral vector. It is noted that while the claims of Trapnell recite re-administration of the vector and DSG, DSG administration is only provided for a certain period of time and then discontinued (see page 33, last paragraph).

Therefore, the claimed invention is anticipated by Trapnell et al.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 25 is newly objected to under 37 CFR 1.75 as being a substantial duplicate of claim 28. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case claims 25 and 28 are duplicates of each other, and both depend from claim 16. This new ground of rejection was necessitated by the addition of claim 28.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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